Combinative Nicotinic/D1 Agonism Therapy for the Treatment of Alzheimer's Disease

This application claims the benefit of priority of United States Provisional Application Number 60/422,047 filed on October 29, 2002.

FIELD OF THE INVENTION

The invention involves the fields of medical and pharmaceutical sciences. The invention further involves the treatment of medical conditions using a combination of pharmaceutical compounds. In particular, the invention involves the treatment of the cognitive dysfunction in Alzheimer's disease.

BACKGROUND OF THE INVENTION

Alzheimer's disease is a progressive disorder that slowly kills nerve cells in the brain. Symptoms of Alzheimer's disease include personality changes, memory loss and impairment, dementia, language difficulties, and decline in abstract thinking. These symptoms can be referred to broadly as cognitive dysfunction.

While the benefits of combinative therapies are well known, such therapies have either not been fully exploited or have not been successfully applied to date in the treatment of Alzheimer's disease. Thus, there is a need in the art for more effective therapies for the treatment of Alzheimer's disease. The use of multiple compounds to treat an indication can increase the beneficial effects while reducing the presence of side effects.

BRIEF SUMMARY OF THE INVENTION

In one embodiment the invention provides a combination for the treatment of Alzheimer's disease comprising an alpha-7-nicotinic agonist and a D1 receptor agonist,

wherein the alpha-7-nicotinic agonist and the D1 receptor agonist together comprise a therapeutically effective amount of the alpha-7-nicotinic agonist and the D1 receptor agonist. The combination can be a single dosage form.

Another embodiment of the invention provides a method of treating Alzheimer's disease in a subject comprising administration to the subject a combination comprising an alpha-7-nicotinic agonist and a D1 receptor agonist, wherein the alpha-7-nicotinic agonist and the D1 receptor agonist together comprise a therapeutically effective amount of the alpha-7-nicotinic agonist and the D1 receptor agonist. The administration of each of the alpha-7-nicotinic agonist and the D1 receptor agonist can occur sequentially within about 24 hours, about 12 hours, about 6 hours, about 3 hours, and about 1 hour. The administration of each of the alpha-7-nicotinic agonist and the D1 receptor agonist can occur substantially concomitantly.

Another embodiment of the invention provides a method of treating Alzheimer's Disease in a subject comprising administration to the subject of an alpha-7-nicotinic agonist daily and administration to the subject of a D1 receptor agonist on a cyclic basis. A cyclic basis of D1 receptor agonist can comprise (a) administering the D1 receptor agonist for about 7, 14 or 21 days; (b) not administering the D1 receptor agonist for about 7, 14, or 21 days; and (c) repeating steps (a) and (b) one or more times.

DETAILED DESCRIPTION OF THE INVENTION

It is likely that the cognitive/dementia symptoms that are characteristic of Alzheimer's disease reflect not only a deterioration in cholinergic systems of the basal forebrain, but also an age-related concomitant progressive decline in frontostriatal function,

in part related to a reduction of dopamine signaling in these regions. A combination therapy that encompasses properties of both alpha-7-nicotinic agonism and D1 agonism can serve to enhance the quality of life and delay the progression of cognitive decline and onset of dementia in this patient population.

At present, there is no effective treatment for cognitive loss or the prevention of the onset of dementia in Alzheimer's disease. The invention provides a combination drug therapy for subjects with Alzheimer's disease. This combination drug therapy delays the progression of cognitive decline and onset of dementia and other symptoms in subjects with Alzheimer's disease.

One aspect of the invention involves a method for improving cognitive dysfunction and delaying the onset of dementia in a subject diagnosed with Alzheimer's disease. Such a method can involve administering to the patient a pharmaceutical composition comprising an alpha-7-nicotinic agonist and a pharmaceutical composition comprising a D1 receptor agonist.

One embodiment of the invention provides a combination drug therapy for subjects with Alzheimer's disease. The therapy can comprise an optimal combination comprising a first amount of an alpha-7-nicotinic agonist and a second amount of a D1 receptor agonist, wherein the alpha-7-nicotinic agonist and the D1 receptor agonist together comprise a therapeutically effective composition.

Compounds of the Invention

Alpha-7-Nicotinic Agonists

Examples of alpha-7-nicotinic agonists include, for example, galantamine, nicotine transdermals (Elan; Novartis; Alza), altinicline (Merck & Co.; a subtype-selective nicotinic

acetylcholine receptor (nAChR) ligand; altinicline is the active isomer of SIB-1765F (fumarate salt) which activates central nAChR (J Pharm Exp Ther, 1996, 280, 384)); RJR-2403 (Targacept, Aventis); FK-236924 (Fujisawa; FK-236924 is a linoleic acid derivative), Pharmaprojects No. 5147 (Japan Tobacco; this is a representative compound in a series of diazabicyclo[3.3.1]nonane derivatives; see WO9630372); Pharmaprojects No. 4807 (Lundbeck; a series of carbamoyloxyamine compounds that act selectively at central nicotine acetylcholinesterase receptors (nAChRs); see WO9608468); S-1663 (Merck & Co,.; S-1663 is a nicotinic cholinergic channel modulator); A-84543 (Abbott; A-84543 is a lead compound in a series of nicotinic cholinergic channel activators based on a heteroaryl ether); ABT-089 (Abbott); ABT-418 (Abbott; ABT-418 is an isoxasole bioisostere which acts as a nicotinic cholinergic channel activator; see Drug Dev Res, 1997, 40, 304; A-82695 (the N-dimethyl analogue of ABT-418) is also being studied, see 207th ACS (San Diego), 1994, MEDI 176); Pharmaprojects No. 6592 (Abbott; neuronal nicotinic receptor ligands, a series of 3-(2-aminoethoxy) pyridine derivative nicotinic agonists have been identified, see 222nd ACS (Chicago), 2001, MEDI 42); Pharmaprojects No. 6336 (Biofrontera, Johnson & Johnson); and pharmaceutically acceptable salts thereof. See Pharmaprojects, August 2002, PJB Publications Ltd.

D1 receptor agonists

D1 receptor agonists of the invention include, for example, fenoldopam (Elan, Beaufour-Ipsen, Biovail; see Clin Pharmacol Ther, 1987, 41, Abs 111 A-6); pergolide mesylate (Lilly; see Movement Disorders, 1992, 7 (Suppl 1); Abs P276; Br Med J, 1982, II, 465); adrogolide hydrochloride (DrugAbuse Sciences; adrogolide hydrochloride is the

diacetyl prodrug of A-86929, see 1st Eur Cong Pharmacol (Milan), 1995, Abs p108; FASEB J, 1995, 9(3), Abs 2284-5; analogues of A-86929 were synthesized and showed potency and selectivity for D1 (210th ACS (Chicago), 1995, MEDI 133)), A-77636 (dopamine D1 selective agonist with potential as an antiparkinsonian, which was under development by Abbott (Scrip, 1995, 2060, 25), fenoldopam prodrugs (GlaxoSmithKline, Elan); propylbutyldopamine (GlaxoSmithKline; see Pharmacologist, 1983, 25, Abs 487); SK&F-77434 (GlaxoSmithKline; SK&F-77434 is a 3N-allyl-benzazepine derivative of SK&F-38393, see 10th Int Cong Pharmacol (Sydney), 1987, Abs P211; 16th CINP Cong (Munich), 1988, Abs 10.31.02); SK&F-R-87516 (GlaxoSmithKline; see Pharmacologist, 1985, 27(3), Abs 328; Fed Proc, 1986, 45(3), Abs 1548; Proc Br Soc Pharmacol (Oxford), 1987, Abs C-140); BAM-1110 (Maruko Seiyaku; see Movement Disorders, 1992, 7(Suppl 1), Abs P157); YM-435 (Mochida; see 41st ASPET (Milwaukee), 1990, Abs 256; 42nd ASPET (San Diego), 1991, Abs 369); dihydrexidine (Indevus; see WO9600062); propylbutyldopamine (Cornell; see 2nd World Conf Clin Pharmacol Ther (Washington), 1983, Abs 329; Hypertension, 1984, 6 (Suppl 1), Abs I-40 to I-45); CY-208-243 (Novartis; see Life Sci, 1988, 42(2), 137; Proc Br Pharmacol Soc (Dublin), 1988, Abs C113, C115, 560P & 562P; 16th CINP Cong (Munich), 1988, Abs 10.31.02); etisulergine (Novartis; see J Neural Transm, 1981, 51, 39); dopamine agonists (Parke-Davis, Pfizer; see J Med Chem, 1988, 31, 688); cianergoline (Pharmacia; 10th Meet Int Soc Hypertension (Interlaken), 1984, Abs 259, 584, 585 and 788); Z-1046 (Zambon; see 12th Int Cong Pharmacol (Montreal), 1994, Abs P1.9.60 & P1.9.61; further 2-aminotetrahydronaphthalenes are claimed in WO9608228, WO9608463 and WO9608489); Z-11410 (Zambon; see 212th ACS (Orlando), 1996, MEDI 147); analogues of nomifensine with DA1 agonist activity (GlaxoSmithKline; see J Med

Chem, 1987, 30, 1454); and pharmaceutically acceptable salts thereof. See Pharmaprojects, August 2002, PJB Publications Ltd.

Combinations of Compounds of the Invention

One or more alpha-7-nicotinic agonists can be combined with one or more D1 receptor agonists, for example, in a single dosage form or in separate dosage forms to be administered sequentially. Alternatively, one compound can function both as a alpha-7-nicotinic agonist and as a D1 receptor agonist.

Methods of Treating Alzheimer's Disease

Combination therapy, as used herein, is the administration of one or more alpha-7-nicotinic agonists and one or more D1 receptor agonists sequentially, substantially sequentially, and/or concomitantly in a regimen that will provide beneficial effects of the drug combination. Alternatively, the administration of one or more alpha-7-nicotinic agonists and one or more D1 receptor agonist can occur substantially cyclically. For example, one or more alpha-7-nicotinic agonists can be administered on a daily basis, while one or more D1 receptor agonists can be administered on a cyclic basis. A cyclic basis or cyclically means that the D1 receptor agonist is administered for a certain amount of days and then is not administered for a certain amount of days. The cycle of daily administration and then non-administration can be repeated one or more times. In one example, one or more alpha-7-nicotinic agonists can be administered daily and one or more D1 receptor agonists can be co-administered for about 7, 14 or 21 days. Then, the one or more D1 receptor agonists are not administered for about 7, 14 or 21 days. The cycle of administration/non-administration of the D1 receptor agonists can be repeated cyclically one or more times while the alpha-7-nicotinic agonist administration continues on a daily basis.

In a preferred embodiment, one or more alpha-7-nicotinic agonists can be administered daily and one or more D1 receptor agonists can be co-administered for about 7 days. The one or more D1 receptor agonists are then not administered for about 21 days, while administration of the alpha-7-nicotinic agonists continues. The administration/non-administration cycle can be repeated one or more times.

The one or more alpha-7-nicotinic agonists and one or more D1 receptor agonists are present in therapeutically effective amounts. That is, they are present in amounts that will achieve the goal of treatment of Alzheimer's Disease. In an alternative embodiment, the invention provides one or more compounds that act both as an alpha-7-nicotinic agonist and a D1 receptor agonist and that are present in therapeutically effective amounts. The combination therapy is also useful with adjunctive therapies. For example, the combination therapy of the invention can be used in combination with other drugs useful in the treatment of Alzheimer's Disease.

The invention provides a method of treating Alzheimer's Disease in a subject comprising administration to the subject of a combination comprising a first amount of an alpha-7-nicotinic agonist and a second amount of a D1 receptor agonist, wherein alpha-7-nicotinic agonists and D1 receptor agonists together comprise a therapeutically effective amount of the drugs.

Alzheimer's disease is treated where one or more symptoms are alleviated or reduced, the disease is prevented and/or the disease occurrence is moderated. Treatment also refers to the slowing of the progression of Alzheimer's disease or prophylactically reducing or inhibiting Alzheimer's disease. Symptoms of Alzheimer's disease include, for example, personality changes, memory loss and impairment, dementia, language difficulties,

and decline in abstract thinking. These symptoms can be referred to broadly as cognitive dysfunction.

Each of the doses of alpha-7-nicotinic agonists and D1 receptor agonists can occur within about 24 hours of each other. In other embodiments of the invention each of the doses of alpha-7-nicotinic agonists and D1 receptor agonists can occur within about 12, 6, 3, or 1 hours of each other. Preferably, the doses of the drugs are administered substanitially concomitantly, for example in a single dosage form or in separate dosage forms. While this combinative therapy can be administered as stated above, it should be noted that the one or more D1 receptor agonists can be administered on an cyclic basis and not on a continual basis. For example, the one or more alpha-7-nicotinic agonists can be administered on a daily basis, while the one or more D1 receptor agonists can be administered for about 7 consecutive days per month.

The combination of one or more alpha-7-nicotinic agonists and D1 receptor agonists provide greater than expected results in the treatment of Alzheimer's disease, i.e., greater that the sum of each drug's effect taken separately. The results are greater than those that would be expected from the prior art and provide a significant practical advantage in the treatment of Alzheimer's disease. That is, the inventive compositions and methods provide direct cognitive enhancement and delay the onset of dementia.

Administration Methods

The compositions of the invention can be administered to a subject by any means known in the art. A subject can be an animal, such as a mammal, including, for example, humans and non-human primates. The compositions of the invention can be present in a pharmaceutically acceptable formulation or composition. A pharmaceutically acceptable

composition or formulation comprises one or more alpha-7-nicotinic agonists and/or one or more D1 receptor agonists, and preferably, an acceptable carrier, such as a stabilizer, buffer, and/or the like. The one or more alpha-7-nicotinic agonists and one or more D1 receptor agonists can be administered and introduced into a subject by any standard means, with or without stabilizers, buffers, and the like, to form a pharmaceutically acceptable composition or formulation. Pharmaceutically acceptable formulations or compositions treat a disease state, such as Alzheimer's disease, in a subject.

A pharmaceutically acceptable formulation of the invention can allow for the effective distribution of the compositions of the instant invention in the physical location most suitable for their desired activity for example, the brain. Non-limiting examples of agents suitable for formulation with the compositions of the instant invention include: P-glycoprotein inhibitors (such as Pluronic P85), which can enhance entry of drugs into the CNS (Jolliet-Riant and Tillement, 1999, *Fundam. Clin. Pharmacol.*, 13, 16-26); biodegradable polymers, such as poly (DL-lactide-coglycolide) microspheres for sustained release delivery after intracerebral implantation (Emerich, DF *et al*, 1999, *Cell Transplant*, 8, 47-58) (Alkermes, Inc. Cambridge, MA); and loaded nanoparticles, such as those made of polybutylcyanoacrylate, which can deliver drugs across the blood brain barrier and can alter neuronal uptake mechanisms (*Prog Neuropsychopharmacol Biol Psychiatry*, 23, 941-949, 1999).

The present invention also includes pharmaceutically acceptable compositions prepared for storage or administration, which include the desired compounds in a pharmaceutically acceptable carrier, diluent, or adjuvant. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in

Remington's Pharmaceutical Sciences, Mack Publishing Co. (A.R. Gennaro edit. 1985) hereby incorporated by reference herein. For example, preservatives, stabilizers, dyes and flavoring agents can be provided. These include sodium benzoate, sorbic acid and esters of *p*-hydroxybenzoic acid. In addition, antioxidants and suspending agents can be used.

A pharmaceutically acceptable composition or formulation is in a form suitable for administration into a cell or subject. Suitable forms, in part, depend upon the use or the route of entry, for example oral, transdermal, or by injection. Such forms should not prevent the composition or formulation from reaching a target cell or organ. For example, pharmacological compositions injected into the blood stream should be soluble. Other factors are known in the art, and include considerations such as toxicity and forms that prevent the composition or formulation from exerting its effect.

A pharmaceutically acceptable formulation of the invention can be delivered to a subject by a liposome delivery mechanism. Standard protocols for formation of liposomes can be followed. The compositions of the present invention can also be formulated and used as for example, tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions, suspensions for injectable or inhalation administration.

The pharmaceutically acceptable formulations can be locally delivered by, for example, direct injection or by use of an infusion pump. Direct injection, such as subcutaneous, intramuscular, or intradermal injection, can take place using standard needle and syringe methodologies, or by needle-free technologies such as those described in Conry *et al.*, 1999, *Clin. Cancer Res.*, 5, 2330-2337 and Barry *et al.*, International PCT Publication No. WO 99/31262.

Compositions of the invention can be delivered to a subject by systemic administration. Systemic administration is *in vivo* systemic absorption or accumulation of drugs in the blood stream followed by distribution throughout the entire body. Administration routes that can lead to systemic absorption include, without limitation: intravenous, subcutaneous, intraperitoneal, inhalation, transdermal, oral, intrapulmonary and intramuscular.

The compositions of the invention and formulations thereof can be administered orally, topically, parenterally, by inhalation or spray, or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and/or vehicles. The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (*e.g.*, intravenous), intradermal, intramuscular, or intrathecal injection or infusion techniques and the like.

The pharmaceutical compositions can be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use can be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more such sweetening agents, flavoring agents, coloring agents or preservative agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient or ingredients in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients can be, for example, inert diluents; such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic

acid; binding agents, for example starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets can be uncoated or they can be coated by known techniques. In some cases such coatings can be prepared by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monosterate or glyceryl distearate can be employed.

Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in a mixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents can be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions can also contain one or more preservatives, for example ethyl, or n-

propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions can be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions can contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring agents can be added to provide palatable oral preparations. These compositions can be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents or suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, can also be present.

Pharmaceutical compositions of the invention can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents can be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions can also contain sweetening and flavoring agents.

Syrups and elixirs can be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose. Such formulations can also contain a

demulcent, a preservative and flavoring and coloring agents. The pharmaceutically acceptable compositions can be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compositions of the invention can also be administered in the form of suppositories, *e.g.*, for rectal administration of the drugs. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

Compositions can be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

For administration to non-human animals, the composition can also be added to the animal feed or drinking water. It can be convenient to formulate the animal feed and drinking water compositions so that the animal takes in a therapeutically appropriate

quantity of the composition along with its diet. It can also be convenient to present the composition as a premix for addition to the feed or drinking water.

A pharmaceutically effective dose is that dose required to treat a disease state such as Alzheimer's Disease. The pharmaceutically effective dose depends on the type of disease, the composition used, the route of administration, the type of mammal being treated, the physical characteristics of the specific mammal under consideration, concurrent medication, and other factors that those skilled in the medical arts will recognize.

An alpha-7-nicotinic agonist and a D1 receptor agonist can each be present in a dose of about 1 to about 10,000 mg/day, of about 10 to about 10,000 mg/day, of about 25 to about 500 mg/day, of about 50 to about 200 mg/day, or about 0.25 mg to about 50 mg/day. In a preferred embodiment of the invention the dosage range of each of the alpha-7-nicotinic agonist and the D1 receptor agonist is from about 10^{-6} to 10^{2} mg/kg/day. The amount of active ingredient that can be combined with any carrier materials to produce a single dosage form or separate dosage forms varies depending upon the host treated and the particular mode of administration. Dosage unit forms generally contain between from about 0.25 mg to about 1,000 mg of an active ingredient. It is understood that the specific dose level for any particular patient depends upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

All patents, patent applications, and other scientific or technical writings referred to anywhere herein are incorporated by reference. The invention illustratively described herein suitably can be practiced in the absence of any element or elements, limitation or limitations

that are not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of", and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments, optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the description and the appended claims.

In addition, where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.